difference we found was caused by differences in sensitivity to tDCS. Further control experiments of left-handed participants, for instance, are necessary.

The effect of anodal tDCS during right-hand motor imagery increased the most at 15–20 min after stimulation and began to gradually decay, but continued for more than 30 min. The after-effect of tDCS on cortical excitability resembles a long-term potentiation (LTP)-like or long-term depression (LTD)-like mechanism. Several studies using tDCS or other transcranial stimulation methods to induce excitability changes reported a delayed peak in the effect (minutes after the end of stimulation; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Kuo, Grosch, Fregni, Paulus, & Nitsche, 2007; Kuo et al., 2008; Merzagora et al., 2010; Nitsche et al., 2006). Delayed LTP and LTD are also common findings in animal studies (Fernández de Sevilla, Núñez, Borde, Malinow, & Buño, 2008; Raymond, 2007). The similar delay we found probably reflects a physiological LTP-like cortical response to tDCS. The prolonged effect was not seen on mu ERD during left-hand (non-dominant) motor imagery. This may be also because of the lesser effect of tDCS on the non-dominant side.

Care should be taken in interpreting the current results because of the relatively small sample size. However, as a preliminary study, the present data show that cortical excitability is closely related to the ratio of activated and desynchronized neurons during motor imagery, and that: (1) anodal tDCS increased cortical excitability and thus promoted the enhancement of mu ERD; (2) the enhancement of mu ERD following non-dominant hand motor imagery by tDCS was also observed, although it was less than that following dominant hand motor imagery; (3) participants who used their dominant hand daily showed a stronger asymmetric effect of tDCS and a weaker effect on mu ERD during non-dominant hand motor imagery; and (4) the effect of tDCS on mu ERD during dominant hand motor imagery increased the most at 15–20 min after the stimulation and gradually decayed afterward but persisted for more than 30 min. However, the effect of tDCS on mu ERD during non-dominant hand motor imagery increased immediately and decayed rapidly. These results suggest that the background excitability of M1 may determine the strength of the effect of anodal tDCS on ERD by hand motor imagery and the greater excitability of M1 promotes larger effects of tDCS on ERD. Considering the possibility that BCI neurofeedback training with active physical therapy or with functional electric stimulation may improve the motor abilities of chronic stroke patients (Broetz et al., 2010), it might also be effective to combine tDCS with BCI training to improve BCI training's effectiveness.

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J Rehabil Med 2014 Preview

CASE REPORT

EFFICACY OF BRAIN-COMPUTER INTERFACE-DRIVEN NEUROMUSCULAR ELECTRICAL STIMULATION FOR CHRONIC PARESIS AFTER STROKE

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Objective: **Brain computer interface technology is of great interest to researchers as a potential therapeutic measure for people with severe neurological disorders. The aim of this study was to examine the efficacy of brain computer interface, by comparing conventional neuromuscular electrical stimulation and brain computer interface-driven neuromuscular electrical stimulation, using an A-B-A-B withdrawal single-subject design.**

Methods: **A 38-year-old male with severe hemiplegia due to a putaminal haemorrhage participated in this study. The design involved 2 epochs. In epoch A, the patient attempted to open his fingers during the application of neuromuscular electrical stimulation, irrespective of his actual brain activity. In epoch B, neuromuscular electrical stimulation was applied only when a significant motor-related cortical potential was observed in the electroencephalogram.**

Results: **The subject initially showed diffuse functional magnetic resonance imaging activation and small electroencephalogram responses while attempting finger movement. Epoch A was associated with few neurological or clinical signs of improvement. Epoch B, with a brain computer interface, was associated with marked lateralization of electroencephalogram (EEG) and blood oxygenation level dependent responses. Voluntary electromyogram (EMG) activity, with significant EEG–EMG coherence, was also prompted. Clinical improvement in upper-extremity function and muscle tone was observed.**

Conclusion: **These results indicate that self-directed training with a brain computer interface may induce activity-dependent cortical plasticity and promote functional recovery. This preliminary clinical investigation encourages further research using a controlled design.**

Key words: brain computer interface; stroke; hemiparesis; neuromuscular electrical stimulation; rehabilitation.

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INTRODUCTION

Brain-computer interface (BCI) technology is a newly developed technique that is attracting much attention. Recent studies have shown that brain signals measured using electroencephalography (EEG) or magnetoencephalography (MEG) provide information for the presumption of motor intention (1). Using BCI technology, real-time feedback concerning cortical activity can be provided to the patient through visual and somatosensory information.

In the present study, we developed a BCI system controlling neuromuscular electrical stimulation (BCI-driven NMES) as a closed-loop feedback system for use with severe paresis, and examined whether there were advantages of a closed-loop BCI system compared with an open-loop NMES system to restore motor ability. We used a single-subject A-B-A-B experimental design, and employed a series of neurological and clinical assessments to comprehensively evaluate improvement of the motor system. Upstream to downstream measures were used, including regional cerebral electric and blood oxygenation responses, corticospinal connectivity, voluntary muscle activity, kinetic performance, and muscle tone. The reproducibility of neurophysiological changes simulated by BCI was also evaluated.

CASE REPORT

A 38-year-old right-handed Japanese male, with severe chronic left hemiplegia due to right putaminal haemorrhage 14 months earlier, was the subject of this study. The patient had already received 7 months of inpatient rehabilitation after the onset of putaminal haemorrhage, including the last 2 months in Keio Tsukigase Rehabilitation Center (KTRC), and following 7 months of outpatient rehabilitation. Rehabilitation examination at hospital admission revealed that the patient's upper limb section of the Fugl-Meyer assessment (FMA) score for testing physical motor performance at the paralysed upper extremity

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was 27 (range 0–66), and his modified Ashworth scale (MAS) score for testing muscle spasticity at the paralysed finger was 2 (range 0–4). These scores were unchanged from those acquired 8 months prior to admission to the present study, including 30 days of previous inpatient rehabilitation in KTRC. His hand function was severely impaired, and surface electromyogram (EMG) activity from the affected extensor digitorum communis (EDC) was absent. Sensory examination showed a mild decrease in position sense in all fingers. Pin-prick and touch senses were also mildly impaired. He was independent in activities of daily living, and used a T-cane and plastic ankle-foot orthosis. His cognitive abilities were intact. Before the experiment, the patient gave written informed consent to participate in this study. The only medication that the patient received was hypnotic, and no anti-spasticity drugs were used during inpatient rehabilitation.

The experimental design described below followed the Declaration of Helsinki on medical protocol and ethics, and was approved by the Keio University School of Medicine ethics committee.

Experimental design

The study incorporated a within-subject A-B-A-B withdrawal design in which we alternated epochs A (control) and B (BCI). During epoch A, the patient was asked to attempt finger opening for 3 s at maximal voluntary effort. During this period, simultaneous NMES (see Appendix S1[1]) was applied to the paralysed finger-opening muscle. Next, a 3-s rest period was given, and stimulation was halted. The trial lasted for 6 s and was repeated for 60 min, and was conducted on weekdays for 2 weeks (10 days in total).

During epoch B, the patient was similarly asked to attempt finger opening for 3 s at maximal voluntary effort. The BCI monitored motor-related cortical potential in the electroencephalogram (EEG) recorded over the sensorimotor area in the affected hemisphere, and NMES was given only if the amplitude of motor-related cortical potential reached a pre-determined threshold, and amplitude was maintained for 1 s (Fig. 1). A relative power decrease in the sensorimotor rhythm from baseline, called event-related desynchronization (ERD), is known as a biomarker of the excitability of the primary motor area (2). We used ERD as a trigger source of NMES to form the closed-loop structure, which couples continuous motor-related brain activity with somatosensory activity by NMES. The detailed settings for the EEG recordings and the calculation have been described previously (3), and are summarized in Appendix S1[1]. As the training settings of the BCI-NMES and the NMES were different, the subject was not blinded to the training contents.

The experiment was discontinued for the day if the patient reported exhaustion. The subject ended the treatment early on 3 days: 2 in the first BCI epoch and 1 in the second BCI epoch. In both epochs, traditional occupational therapy (OT) was performed 40 min/day after each intervention, which included thermotherapy, continuous muscle stretch, and practicing functional activities (i.e. wiping or holding paper down).

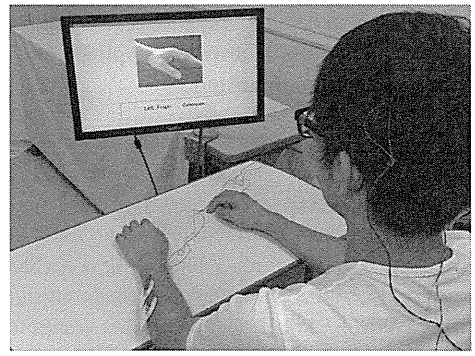

Fig. 1. Training with brain computer interface–neuromuscular electrical stimulation. The subject attempted to extend his fingers according to the instructions presented on the monitor. Electrical stimulation was triggered if the amplitude of the motor-related cortical potential reached a pre-determined threshold.

The patient cancelled OT only once, in the first BCI epoch; he did not end OT early during the NMES epochs. No additional exercise apart from OT was performed during the epochs.

Outcome measures

The following functional magnetic resonance imaging (fMRI), EEG, surface EMG of the affected EDC muscle, and clinical evaluations were performed before the first session and at the end of each training epoch. The researchers involved in the analyses of fMRI, EEG and EMG were blinded as to the training contents.

fMRI data acquisition. Whole-brain fMRI (Excelart/Vantage, Toshiba Medical Systems, Tokyo, Japan) was performed at 1.5 T, with standard scanning software, on the day of admission and the last days of each training period. The following parameters were used for fMRI experiments: repetition time (TR)/echo time (TE)/flip angle 3000 ms/40 ms/90°; field of view 256 mm; matrix size 96 × 96; and slice thickness 5 mm (slice gap 1 mm). Between repetitions, 23 axial sections (slices) were acquired in a continuous manner (i.e. 23 slices per 3 s).

Motor task paradigm. The paradigm was a block design (5 rest and 5 task blocks, 30 s each). We employed a self-paced movement paradigm at 1 Hz, in which the subject was directed to employ self-paced finger-extension movements with the affected hand for 30 s with maximal effort (4). To observe unintentional movement of other muscles, direct observation was performed, as described previously.

fMRI data analysis. Data were processed using a general linear model using Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK). The detailed methods for fMRI data analysis are shown in Appendix S1[1].

EMG analysis. Surface EMG was measured using electrodes on the EDC. The percent change in root mean square (RMS) after the task cue to reference (pre-task) RMS was calculated.

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-1785

To examine the change in the RMS ratio, we used the Kruskal-Wallis and Mann-Whitney *U* tests and applied Bonferroni's correction for multiple comparisons.

Corticomuscular coherence. Corticomuscular coherence (CMC) measures the functional coupling between the cortex and muscle. (5) The details of the coherence calculation are shown in Appendix S1[1]. Coherence is expressed as a real number between 0 and 1, with 1 indicating a perfect linear association. EEG-EMG coherence was considered significant when it was within >95% confidence limits computed from the number of epochs (epochs 100; limit 0.030).

Clinical evaluation. For evaluation of motor function, the upper extremity section of FMA was performed. Finger spasticity was measured using the MAS. Evaluation was performed by a physician and an occupational therapist who were both blinded to the experimental design.

RESULTS

Functional magnetic resonance imaging changes

fMRI activation during affected hand movement prior to training sessions was associated with extensive participation of active areas in both hemispheres, including the bilateral primary motor cortex, primary sensory cortex, supplementary motor area (SMA), and the bilateral premotor cortices (Fig. 2A). The total activated area gradually decreased through the training epochs, and in the BCI-NMES epochs (B1 and B2), lateralization of the activated area was observed. The calculated laterality index (LI) of voxels in the bilateral precentral gyrus and hemisphere was unchanged or decreased during the NMES epoch, while it was markedly increased during the BCI-driven NMES epoch (Fig. 2B–G).

Neurophysiological changes

The ERD in the right primary sensory-motor cortex (SM1) gradually increased during the training epochs, both in the alpha (mu) and beta bands (Fig. 3A). In the time-frequency map before the training epochs, the generation of ERD was not evident by motor intention. In contrast, the time-frequency map on the last day clearly showed ERD in alpha (mu) and beta bands (Fig. 3B). Similar to the fMRI study, the LI of the bilateral SM1 markedly increased only during the BCI-NMES epoch (Fig. 3C). The success rate of triggering NMES by ERD gradually increased during the BCI-NMES epoch (Fig. 3D).

The change in the averaged ratio of RMS of surface EMG activity on the EDC during the task to initial baseline was cal-

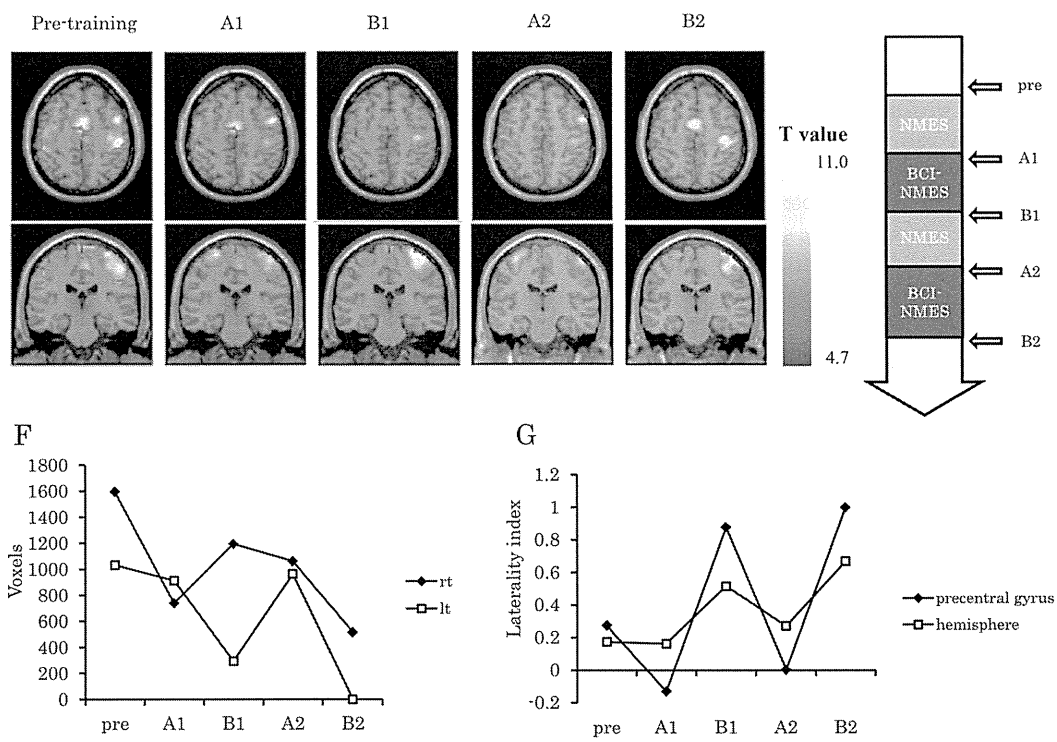

Fig. 2. Change in the pattern of functional magnetic resonance imaging (fMRI) activation during finger movement. (A) Before the start of intervention, fMRI showed diffuse activation including bilateral primary motor cortex, primary sensory cortex, supplemental motor area (SMA), and part of the frontal and parietal lobes. (B) After the first epoch A (NMES), no changes were observed. (C) After the first epoch B (brain computer interface–neuromuscular electrical stimulation; BCI-NMES), brain activity was lateralized to the right hemisphere. (D) However, lateralization of activity was cancelled during the second epoch A. (E) After the second epoch B, fMRI activation was mostly localized to the right primary cortex and SMA. (F) The activated area in the bilateral primary motor area gradually decreased. Laterality index (LI) markedly increased during the BCI-NMES epoch, whereas it decreased during the NMES-only epoch. Hemispheric LI showed a similar pattern, and a tendency of gradual increase (G). MRI Images (A–E) are displayed in neurological convention (left is left).

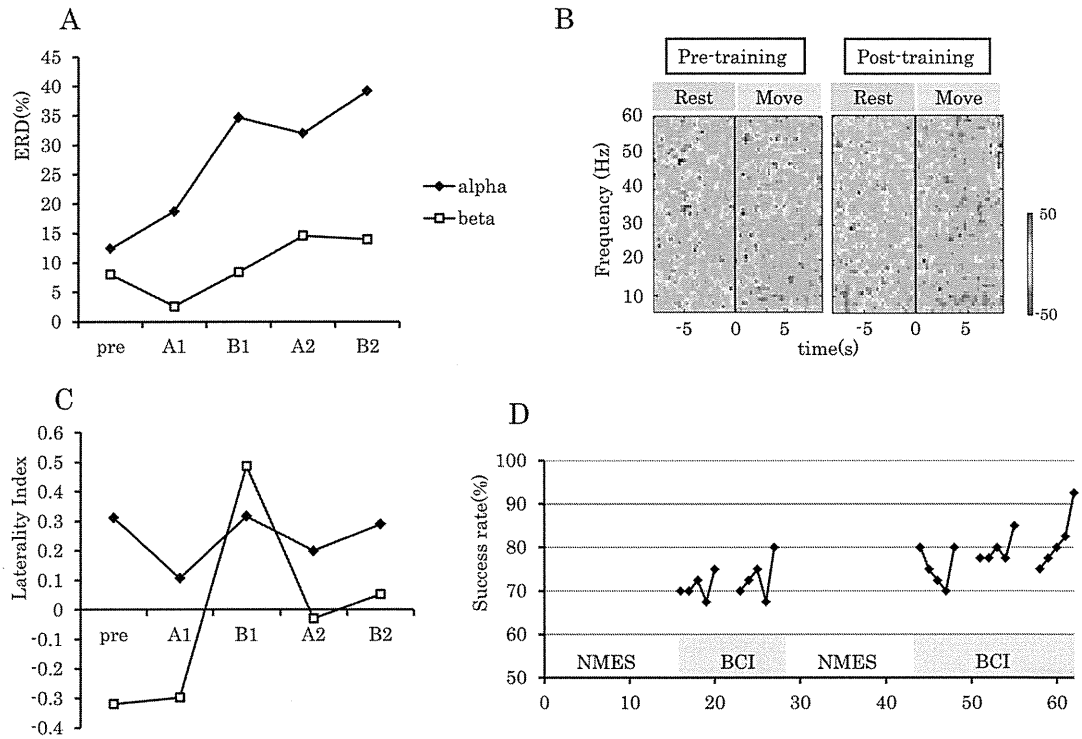

Fig. 3. Time course of electroencephalogram activity. (A) The extent of event-related desynchronization (ERD) in the alpha (mu) and beta bands around SM1 was gradually increased through the training periods. (B) The time-frequency map of ERD over the right cortex before the session started showed limited ERD at both bands during motor intention, while the occurrence of ERD was markedly clear in the map at the end of the whole experiment. The colour bar shows the power spectrum density. Blue indicates low power and red high power. (C) The laterality index of ERD was increased during the brain computer interface–neuromuscular electrical stimulation (BCI-NMES) epoch, showing movement of activity to the right hemisphere. In contrast, laterality index was decreased during the NMES epoch. (D) The success rate of the task gradually increased through the BCI-NMES epoch.

culated (Fig. 4A). There was very little increase (3%) in EMG activity of the EDC by the "extend finger" instruction on the day before training started. After the first NMES epoch, there was a 37% increase in RMS value. After the first BCI epoch, the value reached a 132% increase compared with baseline. However, the RMS ratio on the last day of the second NMES

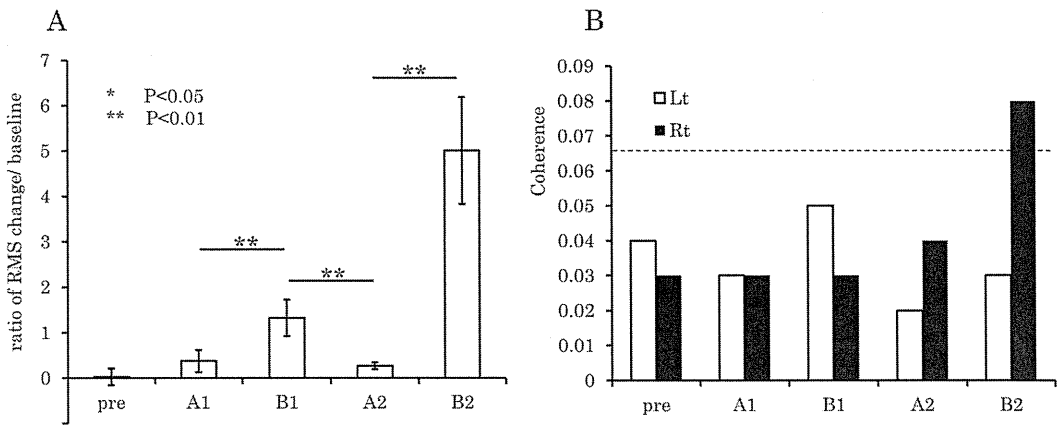

Fig. 4. Change in electromyogram (EMG) activity of extensor digitorum communis (EDC), and corticomuscular coherence (CMC). Prior to the neuromuscular electrical stimulation (NMES) epoch, almost no increase in root mean square (RMS) was observed for attempted finger extension. After the first NMES epoch, a slight increase in RMS was observed, while the second NMES session resulted in a decreased RMS value. (A) In contrast, a marked increase in RMS was observed during the NMES epoch. CMC was calculated using the EEG of SM1 and the EMG of EDC, and was not significant at the start of the training sessions. (B) After the second brain computer interface–neuromuscular electrical stimulation (BCI-NMES) epoch, CMC was significantly increased. Pre: before the start of intervention; A1: after the first epoch A (NMES); B1: after the first epoch B (BCI-NMES); A2: after the second epoch A; B2: after the second epoch B.

Table I. *Clinical scores during conventional neuromuscular electrical stimulation and brain computer interface–neuromuscular electrical stimulation (BCI-NMES) training*

	Before	A1	B1	A2	B2
MAS	2	2	1+	1+	1
FMA U/E	26	27	31	31	34

MAS: modified Ashworth Scale; FMA U/E: upper extremity section of Fugl-Meyer assessment; Before the start of intervention; A1: after the first epoch A (NMES); B1: after the first epoch B (BCI-NMES); A2: after the second epoch A; B2: after the second epoch B.

epoch decreased to 27%. Finally, after the second BCI session, the ratio was increased to 500% relative to the reference EMG.

The CMC in the beta band was calculated using EEG and EMG of the affected EDC (Fig. 4B). The coherence of the EEG in contralateral SM1 and the EMG of upper limb muscles have been shown to be related to functional recovery after stroke (6). Before the sessions started, CMC was not significant. At the end of all sessions, CMC of the left EDC and EEG of the contralateral SM1 exceeded the 95% confidence level.

Clinical changes

The result of the clinical examination of motor function is shown in Table I. The FMA score increased to 34 in the final evaluation, which was mostly achieved during BCI-NMES epochs. This increase in FMA score was not due to improvement in finger function, but was mostly due to improvement in proximal muscle movement in the paretic limb, which was not directly involved in the experimental design. Despite improvement in EMG and EEG activity, no practical finger movement was regained. However, the patient was able to keep his fingers extended and to hold paper down while writing, which was not possible before the intervention. Finger spasticity was reduced from 2 to 1 on the modified Ashworth scale, and this improvement was seen during BCI-driven NMES epochs.

DISCUSSION

The effect of BCI training is often explained by the mechanism of motor learning with closed-loop feedback (7). In our model, the real-time feedback of brain activity was provided with NMES as strengthened proprioceptive feedback. Temporary re-establishment of closed-loop feedback by a BCI system may support the retention of motor-related brain activity after corticospinal tract injury. Furthermore, this BCI-driven NMES system, without visual feedback of brain activity, may indicate the importance of proprioceptive feedback contingent on motor-related brain activity.

Recently, several studies have shown a robust effect of EMG-triggered NMES, which provides closed-loop biofeedback for paralysed limbs (8–10). However, severely hemiplegic patients who show less voluntary EMG cannot use this method. The BCI-NMES could be a substitute for those patients, and may allow some restoration of motor control.

It is possible that the observed changes in EEG or fMRI reflect the simple learning of emerging ERD-like activity, which is independent of practical motor function. However, the observed lateralization of brain activity without any laterality feedback implies that such a simple biofeedback mechanism is not enough to explain the observed changes.

In conclusion, BCI-driven NMES was associated with improvement in motor function and plasticity of the motor cortex in our patient, which was superior to that achieved by NMES only. Although this was a single-subject study, the present data strongly suggest the feasibility of using BCI technology, which accesses the plasticity of the motor system as a whole, from brain to muscle, in stroke rehabilitation. These results encourage further examination with more controlled studies for training with BCIs, especially for severe motor paresis.

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Supplementary material to article by M. Mukaino et al. "Efficacy of brain-computer interface-driven neuromuscular electrical stimulation for chronic paresis after stroke"

APPENDIX S1. Additional information on the experimental settings

Neuromuscular electrical stimulation neuromuscular electrical stimulation (NMES)

A pair of self-adhesive electrodes was placed over the muscle belly of the extensor digitorum communis (EDC) on the paralysed side. NMES (20 Hz, single pulse width 100 μs, 3 s ON, 3 s OFF) was delivered through an electrical stimulator (MEB-2200, Nihon Kohden, Tokyo, Japan). Every day before intervention, the intensity of electrical stimulation was adjusted and fixed at just over motor threshold for evoking visible contraction of EDC muscles (15–20 mA).

Electroencephalography recordings

Electroencephalography (EEG) recordings were made from the scalp near the sensorimotor cortex using 5 silver–silver chloride (Ag-AgCl) surface electrodes with a diameter of 10 mm placed at C3 (left) and C4 (right), defined by the international 10–20 system, and their 20 mm front, back, left lateral, and right lateral positions. The reference electrode was placed at A2 (right earlobe). An additional electrode was placed at A1 (left earlobe) as a ground electrode. EEG was amplified (×50,000) and band-pass filtered (0.5–100 Hz) using a commercially available bioamplifier (g.USBamp, g.tec, Graz, Austria). A Laplacian transformation with 5 electrodes in each hemisphere was used to produce a signal of estimates of current source density for precise cortical activity detection. Signals produced from the left and right hemispheres were digitally sampled at a sample frequency of 1,024 kHz with 12-bit resolution, and were stored on the hard disk of a personal computer.

Calibration of brain computer interface in epoch B

At the beginning of the intervention in epoch B, 40 trials of the cue-based motor task were conducted as a rehearsal, and the parameters of the event-related desynchronization (ERD) detection algorithm in brain computer interface (BCI) were calibrated using the obtained data. During the rehearsal, an arrow pointing to the left ("attempting paretic finger extension") or no arrow (rest) was displayed for 1 s over a cross-shaped icon in the centre of a monitor, and the subject performed the cued task for the next 4 s. Twenty trials per class were given in a randomized order. A 4-dimensional feature vector (the power spectrum densities in alpha (mu) and beta frequency bands in the left and right hemispheric EEGs) was calculated every 30 ms, with a time-sliding window of 1 s during the task. The feature vectors with annotations of either "attempting finger extension" or "during rest" were mapped onto the feature space, and the parameters in the linear discriminant analysis (LDA) algorithm were optimized using g.BSanalyze software (g.tec Guger Technologies, Graz, Austria) to separate the features into appropriate classes. Consequently, the LDA returned either the value "+1" (resting) or "–1" (finger extension) every 30 ms according to the EEGs.

Outcome measures

Functional magnetic resonance imaging analysis. The first 5 images (for 15 s) of each set were discarded, because they showed irregular contrasts acquired before the MRI signal had reached an equilibrium state. Next, motion correction was performed by realigning all the functional volumes to the first volume of the functional series, and by co-registration to the anatomical volume. All co-registered images were normalized to the Montreal Neurological Institute template. After normalization, images were smoothed with a Gaussian kernel (full-width at half-maximum, 8 mm). We estimated the task-specific effects using the general linear model with a delayed boxcar waveform. The boxcar waveform was convolved with the canonical haemodynamic response function. Significance was determined on a voxel-by-voxel basis using a *t*-statistic, which was then transformed to a normal distribution. The resulting sets of spatially distributed *Z*-values constitute statistical parametric maps (SPM{*Z*}), which show regions of significant condition-associated signal changes. These regions were then displayed with a statistical threshold based on the amplitude ($p<0.05$ corrected for multiple comparisons). The voxels with a greater *Z*-value were regions for which blood oxygenation level dependent signal enhancement, caused by changes in blood oxygenation, occurred in accordance with the task. Laterality index (LI) was calculated for the voxels within the whole hemisphere and precentral gyrus.

EEG analysis. The time-frequency map of ERD on the day of admission and the last day of each training period was calculated to examine the change in the value of ERD. ERD was defined as the decrease in the power spectrum relative to the reference period, and the ERD value was defined by the following equation:

$$\mathrm{ERD}(f,t)=\frac{R(f)-A(f,t)}{R(f)}$$

where A(f,t) is the power spectrum of the EEG at frequency f at time t, with reference to the onset of motor intention, and R(f) is the power spectrum of a 1 s epoch of the reference period in each trial. Using this definition, ERD was expressed as a positive number in this study.
As stated above, the computer program returned the result of LDA, either "+1" (resting) or "–1" (finger extension) according to the EEGs. Classification accuracy during training was calculated.

Corticomuscular coherence. EEG and EMG signals during the "finger extension" state were segmented into artefact-free epochs of 1 s duration without overlapping (a total of 100 epochs). To measure the linear correlation between EEG and EMG, coherence was calculated using a fast Fourier transform algorithm with a frequency resolution of 1 Hz, according to the following equation:

$$|R_{xy}(i)|^2=\frac{|f_{xy}(i)|^2}{|f_{xx}(i)\times f_{yy}(i)}$$

In this equation, fxx(i) and fyy(i) are autospectra of the EEG and EMG signals, x and y, for a given frequency (i), and the fxy(i) is the cross-spectrum between them.

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State of intracortical inhibitory interneuron activity in patients with chronic stroke

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HIGHLIGHTS

- Relationships between short intracortical inhibition (SICI) and lesion site, time from onset, and motor function were studied in chronic stroke patients with severe to moderate upper extremity paresis.
- Affected-side SICI had inverse correlations with paretic finger motor function and time from onset.
- The state of intracortical inhibitory neuron activity depends on the state of motor function and lesion site even in chronic stroke patients with severe hemiparesis.

ABSTRACT

Objectives: Few studies have assessed short intracortical inhibition (SICI) in the affected hemisphere (AH) in a large number of patients with chronic stroke. In this study, SICI was assessed in chronic stroke patients with severe hemiparesis, and its relationship to clinical parameters was examined.
Methods: The participants were 72 patients with chronic hemiparetic stroke. SICI of both the AH and the unaffected hemisphere (UH) was assessed. The relationships between SICI and the location of lesion, time from onset, and finger function were studied. Motor function of the paretic finger was assessed with the Stroke Impairment Assessment Set (SIAS) and the Fugl-Meyer test upper extremity motor score. To compare the results with those of healthy subjects, SICI was assessed in seven age-matched control subjects.
Results: MEPs of the UH were evoked in all 72 subjects, and MEPs of the AH were evoked in 24 subjects. SICI of the AH was inversely correlated with paretic finger motor function and time from stroke onset. SICI of the UH was not correlated with either one. SICI of the UH was higher in the cortical lesion group than in the control group.
Conclusions: The state of intracortical inhibitory neuron activity depends on the state of motor function and lesion site even in chronic stroke patients with severe hemiparesis.
Significance: The inhibitory system of the AH is involved in functional recovery of the paretic hand even in the chronic stage of stroke.

1. Introduction

As neurophysiological and functional imaging techniques have progressed, it has been suggested that the brain is capable of extensive functional plasticity after stroke (Cramer et al., 2011). Bütefisch et al. (2000) showed that training-induced changes were related to decreased GABAergic inhibition within intracortical circuits. In humans, this GABAergic inhibitory system can be assessed with a paired-pulse transcranial magnetic stimulation (TMS) technique, in which a conditioning TMS pulse below the threshold for eliciting a motor evoked potential (MEP) inhibits a suprathreshold test stimulus at short intervals (1–5 ms) (Kujirai et al., 1993). This inhibition was called short intracortical inhibition (SICI) (Sanger et al., 2001). Several studies support the notion that modulation of intracortical inhibition contributes to plasticity in the primary motor cortex. It seems that the inhibitory circuit in the primary motor cortex plays an important role in functional reorganization in stroke patients (Shimizu et al., 2002; Manganotti et al., 2002; Liepert et al., 2000).

Some studies have shown that the intracortical inhibitory systems of the affected hemisphere (AH) and the unaffected hemisphere (UH) were disturbed in patients with acute stroke, and this disturbed SICI changed with time from the acute phase to the subacute phase (Shimizu et al., 2002; Liepert et al., 2000). Swayne et al. (2008) showed that SICI correlated with clinical function at 3 months after stroke onset, but not in the acute period, and

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these correlations were no longer present at 6 months. There is, however, little information about SICI in the chronic phase, over 6 months from stroke onset. Few researchers have studied SICI in the AH of patients with chronic, severe, hemiparetic stroke.

Recently, constrained induced movement therapy (CIMT) (Wolf et al., 1989), active–passive bilateral therapy (APBT) (Stinear et al., 2008), and hybrid assistive neuromuscular dynamic stimulation therapy (HANDS) (Fujiwara et al., 2009) were developed for improvement of upper extremity function in patients with chronic stroke. These newly developed therapeutic approaches improved upper extremity function and induced cortical plastic change, confirmed with TMS. Liepert (2006) showed that CIMT induced enlargement of the paretic hand mapping area in the affected-side motor cortex. Stinear et al. (2008) showed that APBT increased affected-side motor cortex excitability. Fujiwara et al. (2009) showed that HANDS therapy induced reduction of intracortical inhibition in the AH. These studies supported the idea that rehabilitation-induced cortical plastic changes can occur even in the chronic phase of stroke. The mechanism of this cortical reorganization could be explained by reduction of local inhibitory interneurons (i.e. SICI), thus unmasking pre-existing excitatory connections (Jacobs and Donoghue, 1991).

The aims of this study were to examine SICI in chronic stroke patients with severe to moderate hemiparesis and to study its relationship to lesion site, time from onset, and motor function.

2. Methods

2.1. Participants

Seventy-two patients (50 males and 22 females) with chronic stroke were recruited for the study from the outpatient clinic. Their mean age was 57.0 ± 14.1 years (range 27–77 years), and their mean time from stroke onset was 28.2 ± 22.6 months (6–104 months). Inclusion criteria consisted of: (1) first-ever stroke; (2) age over 20 years; (3) time from onset more than 6 months; and (4) moderate to severe upper extremity paresis (patients could not move their paretic fingers individually well). Exclusion criteria were: (1) history of major psychiatric or previous neurological diseases, including seizures; (2) cognitive impairment precluding informed consent or the patients Mini Mental Examination Scale score was below 25; and (3) use of central nervous system active drugs. All patients underwent a standardized protocol of inpatient rehabilitation based on physical therapy and occupational therapy in their acute and subacute phases (1–6 months after stroke onset). No patient was still participating in rehabilitation at the time of the study. All patients achieved independence in self-care items and locomotion items of activities of daily living.

Seven age-matched healthy volunteers (5 male, 2 female; mean age 55.9 ± 11.3 years; range 41–66 years) were assessed as a control group.

The purpose and procedures of the study were explained, and informed consent was obtained from all subjects. The study was approved by the institutional ethics review board and performed in accordance with the Declaration of Helsinki.

2.2. Clinical assessment

The brain lesion was localized with computed tomography (CT) or magnetic resonance imaging (MRI). Based on the CT or MRI findings, the patients were divided into two subgroups (cortical and subcortical). Cortical stroke was defined as a lesion located in any cortical area, whether the area was motor cortex or not, and other strokes were defined as subcortical strokes. The subcortical group had lesions located caudal to the corpus callosum, indicating that the corpus callosum was intact. These diagnoses were made by a radiologist.

Motor function of the affected upper extremity was assessed with motor items of the Stroke Impairment Assessment Set (SIAS) (Chino et al., 1995) and the Fugl-Meyer test upper extremity motor score (FM-U) (Fugl-Meyer et al., 1975). The SIAS is a standardized measure of stroke impairment consisting of 22 subcategories, and its reliability and validity have been well demonstrated (Tsuji et al., 2000; Liu et al., 2002). The paretic side motor functions of the upper extremity were tested with the knee-mouth test and the finger-function test. They were rated from 0 (complete paralysis) to 5 (no paresis). The score 1 for the finger test was divided into three subscales: 1a (mass flexion), 1b (mass extension), and 1c (minimal individual movement). The score 3 for finger function means that individual movement of each finger is possible with adequate flexion and extension of the digits; however, the patient carries out the task with severe or moderate clumsiness. The FM-U consists of three categories (A: shoulder/elbow/forearm, B: wrist, C: hand).

2.3. EMG recording

Participants were seated in a reclining chair with the elbow flexed at 70°. Surface electrodes were placed bilaterally on the skin overlying the extensor digitorum communis (EDC) muscles in a bipolar montage (interelectrode distance, 2 cm). Before attaching the electrodes, the skin areas were rubbed with alcohol, and the skin resistance was kept below 5 kΩ. A Neuropack^{TR} electromyography machine (Nihon Kohden Co. Tokyo, Japan) was used to record and analyze the EMG data. The bandpass filter was set at 30 Hz–2 kHz, and the sampling frequency was set to 5 kHz.

2.4. Transcranial magnetic stimulation (TMS)

TMS was delivered with a Magstim 200 magnetic stimulator (The Magstim Company, Whitland, Dyfed, UK). Magnetic stimulation was applied over the motor cortex through a figure-of-eight coil having an external wing diameter of 9 cm and a peak magnetic field of 2.2 T. TMS was delivered to the optimal scalp position for activation of the EDC muscles overlying the left- and right-hand primary motor cortices. The stimulating coil was placed over the optimal site for eliciting responses in the EDC and oriented so that the current in the brain flowed in a posterior to anterior direction through this optimal stimulating site.

Before the examination, the active motor threshold (AMT) and resting motor threshold (RMT) were measured in all participants. Motor threshold was measured with a single pulse from a Magstim 200 connected via a Bistim to a second Magstim 200. RMT was determined according to the recommendation of the International Federation of Clinical Neurophysiology (IFCN) Committee (Rossini et al., 1994). It was defined as the intensity needed to evoke a minimal EMG response (>50 μV) in at least 5 of 10 trials in a relaxed EDC. AMT was defined as the minimum stimulus intensity that produced a motor evoked response (about 200 μV in 5 of 10 trials) during isometric steady EDC contraction of 5–10% maximum, with the help of audiovisual feedback from the EMG.

2.5. Short intracortical inhibition (SICI)

To assess SICI, subthreshold conditioning paired-pulse TMS (Kujirai et al., 1993) was applied. The conditioning and test stimuli were given using the same figure-of-eight coil connected to two magnetic stimulators. The conditioning stimulus was set at 80% of the AMT. The test stimulus was set at 120% of the RMT. The test MEP amplitude was evaluated using a stimulus intensity of 120% RMT with the muscle at rest. Interstimulus intervals (ISIs) were set at 2 and 3 ms, because short ISIs (2–5 ms) inhibit the test

MEP (SICI). Five trials were recorded for each ISI and single-pulse stimulation in pseudorandom order controlled by a laboratory computer. Stimuli were applied every 5 s.

The conditioned MEP peak-to-peak amplitudes were expressed as a ratio to the mean MEP amplitude with test stimulation given alone. The SICI was defined as the mean of these values for the 2- and 3-msec intervals. The SICI was determined in both the AH and the UH. SICI was assessed in the bilateral hemispheres of seven healthy volunteers.

2.6. Statistical analysis

Normality of distribution was examined using the Kolmogorov–Smirnov test. If the data were not normally distributed or ordinal data, non-parametric statistical tests were used. The Mann–Whitney U-test was used to compare non-parametric values between two groups. Unpaired and paired *t*-tests were used to compare parametric values between two groups. Mean values were compared among healthy participants, patients with cortical lesions, and patients with subcortical lesions and analyzed with one-way analysis of variance (ANOVA). If the difference between subjects was significant, post hoc analysis was performed with an unpaired *t*-test. The SIAS and Fugl-Meyer test scores were ordinal data. Time from onset was not normally distributed. Spearman's rank correlation test was used to study possible correlations between SICI and time from onset, the SIAS finger function test, and the FM-U. Correlations of parametric data were tested with Pearson's correlation test. A p value of 0.05 was considered significant for all tests. All statistical analyses were performed with SPSS version 19.0 J.

3. Results

3.1. Clinical details and MEPs of patients with stroke

The clinical details and lesions of the subjects are shown in Tables 1 and 2. The mean F-M score was 28.6 ± 10.9. The median SIAS finger score was 1b.

In all patients with stroke, MEPs were obtained from the UH. MEPs could be elicited from both the AH (0.34 ± 0.48 mV) and the UH (0.56 ± 0.39 mV) in 24 patients (group A). The differences between the AH and the UH in AMT ($p < 0.001$), RMT ($p < 0.001$), and the amplitude of the test MEP ($p = 0.035$) were significant in group A. There was no significant difference in SICI between the AH and the UH in group A ($p = 0.143$). Seven of them had cortical lesions (all of them were infarctions containing the M1 area), and 17 had subcortical lesions (3 corona radiata lacunar infarctions, 5 basal ganglia infarctions, 7 basal ganglia hemorrhages, 2 brainstem infarctions).

In 48 participants, MEPs could only be elicited from the unaffected side (0.45 ± 0.28 mV) (group B). Ten of them had cortical (9 infarction, 1 hemorrhage, all of them contained the M1 area) and 38 had subcortical lesions (10 corona radiata lacunar infarctions, 1 corona radiata hemorrhage, 14 basal ganglia infarctions, 21 basal ganglia hemorrhages, 2 brainstem infarctions).

Table 1
The lesion of stroke.

	Infarction	Hemorrhage	Total
Cortical	16	1	17
Subcortical			
Corona radiata	10	1	11
Putamen	8	19	27
Thalamus	5	8	13
Brain stem	4	0	4
Total	43	29	72

There were significant differences in age ($p = 0.02$), SIAS finger function scores ($p < 0.001$), and FM-U scores ($p = 0.03$) between groups A and B (Table 2). The differences in AMT, RMT, test MEP amplitude, and SICI of the UH were not significant between groups A and B.

3.2. Comparison of subcortical, cortical, and control groups

Fifty-five patients had subcortical lesions and seventeen had cortical lesions, including the primary motor cortex. The mean time from onset was 28.5 ± 22.8 months in the subcortical group and 27.2 ± 22.5 months in the cortical group. The mean FM-U score was 28.3 ± 11.5 in the subcortical group and 29.8 ± 8.8 in the cortical group. The median SIAS finger function score was 1b in both the subcortical and cortical groups. There were no significant differences in time from onset ($p = 0.35$), SIAS finger function score ($p = 0.49$), and FM-U ($p = 0.33$) between the subcortical and cortical groups.

Table 3 shows the TMS parameters of each hemisphere in the subcortical, cortical, and healthy control group. MEPs of the EDC were evoked in both sides in all seven healthy controls. MEPs of the AH were evoked in 17 subjects in the subcortical group and seven subjects in the cortical group. There was a significant main effect of lesion (subcortical, cortical, and control) in AMT of the AH ($F = 12.8$, $p < 0.001$), RMT of the AH ($F = 10.69$, $p < 0.001$), test MEP amplitude of the AH ($F = 10.31$, $p < 0.001$), test MEP amplitude of the UH ($F = 11.86$, $p < 0.001$), and SICI of the UH ($F = 3.35$, $p = 0.04$). AMT and RMT of the AH in the subcortical ($p < 0.001$, $p = 0.001$) and cortical groups ($p = 0.004$, $p = 0.003$) were significantly higher than in the control group, but the difference between the subcortical and cortical groups was not significant. The amplitudes of test MEPs of the AH and UH were significantly smaller in both the subcortical ($p = 0.002$, $p < 0.001$) and cortical groups ($p = 0.002$, $p = 0.002$) than in the control group. The value of SICI of the UH in the cortical group was significantly higher than in the control group ($p = 0.04$). The difference in the SICI of the UH between the subcortical group and the control group was not significant on the post hoc unpaired *t*-test ($p = 0.307$).

Within subcortical strokes, one might suggest that those involving the corona radiata would be likely to affect transcallosal fibers projecting to and from the unaffected hemisphere, whereas clearly those in the putamen, thalamus, or brainstem would not. Therefore, the UH SICI was compared between the 28 patients in whom the cortex and corona radiata were involved (cortical + corona radiata) and the 44 patients in whom the putamen, thalamus, and brain stem (subcortical) were involved. The UH SICIs of the cortical + corona radiata and subcortical were 0.89 ± 0.42 and 0.82 ± 0.37, respectively. There was no significant main effect of lesion (cortical + corona radiata, subcortical, and control) ($F = 2.265$, $p = 0.11$).

3.3. SICI and motor function

As shown in Figs. 1 and 2, SICI of the AH had a significant inverse correlation with time from onset (rs = 0.55, $p = 0.006$), the SIAS finger function test score (rs = 0.61, $p = 0.001$), and the FM-U (rs = 0.37, $p = 0.037$). The SIAS finger function score and FM-U did not correlate with time from onset (rs = 0.091, $p = 0.447$; rs = −0.019, $p = 0.877$). The values of AMT and RMT of both hemispheres did not correlate with time from onset (Figs. 3A and 3B).

There was no significant correlation between SICI of the UH and motor function. SICI of the AH was not correlated with SICI of the UH ($p = 0.08$). The value of SICI was not correlated with the amplitude of test MEP in both the AH ($p = 0.166$) and the UH ($p = 0.267$), suggesting that the observed changes in SICI reflect altered inhibitory activity rather than simply reduced excitability of the corticospinal output.

Table 2
Characteristics and TMS measurements of Group A and B.

	Total			
	(n = 72)	Group A (n = 24)	Group B (n = 48)	p
Age (years)	57 (14.0)	62.9 (14.4)	54.0 (13.1)	0.007
TFO (months)	28.2 (22.5)	29.7 (22.9)	27.5 (22.6)	0.38*
SIAS finger	1b (1a-3)	1c (1a-3)	1b (1a-3)	<0.001*
FM-U	28.6 (10.9)	32.5 (10.5)	26.8 (10.7)	0.03*
AMT UH	40.2 (7.2)	38.2 (7.5)	41.4 (6.8)	0.089
AH		49.3(6.9)		
RMT UH	54.4 (9.8)	53.1 (10.4)	55.3 (9.6)	0.262
AH		65.9(11.8)		
Test MEP UH (mV)	0.48 (0.32)	0.56 (0.39)	0.45 (0.28)	0.131
AH		0.34(0.48)		
SICI UH	0.84 (0.38)	0.85 (0.30)	0.84 (0.43)	0.45
AH		0.77(0.30)		

Abbreviations: TFO, time from stroke onset; TMS, transcranial magnetic stimulation; SIAS finger, Stroke Impairment Assessment Set finger function test; FM-U, Fugl-Meyer test upper extremity motor score; AMT, active motor threshold; RMT, rest motor threshold; UH, unaffected hemisphere; AH, affected hemisphere; MEP, motor evoked potential; SICI, short intracortical inhibition; Values are mean values (SD), the value of SIAS finger is median score (range). p values were calculated with the unpaired t test.
* p values were calculated with Mann–Whitney U-test.

Table 3
TMS parameters of subcortical, cortical and control group.

		Subcortical group (UH n = 55, AH n = 17)	Cortical group (UH n = 17, AH n = 7)	Control (n = 14)	F	p
Age (years)		57.1(13.9)	56.8 (15.2)	55.9(11.3)	0.003	0.953
AMT (%)	AH	49.4 (7.0)	49.0 (6.1)	38.2 (5.9)	12.804	<0.001
	UH	40.7 (6.8)	38.6 (7.1)	38.2(5.9)	1.125	0.33
RMT (%)	AH	65.0 (9.2)	67.8 (15.4)	50.8 (6.3)	10.692	<0.001
	UH	55.2 (9.0)	51.7 (10.3)	50.8 (6.3)	1.885	0.158
Test MEP (mV)	AH	0.38 (0.52)	0.20 (0.08)	0.95 (0.34)	10.314	<0.001
	UH	0.47 (0.32)	0.52 (0.34)	0.95(034)	11.868	<0.001
SICI	AH	0.83 (0.33)	0.91 (0.32)	0.63 (0.19)	2.724	0.075
	UH	0.80 (0.38)	0.96 (0.34)	0.63(0.19)	3.357	0.04

Abbreviations: TMS, transcranial magnetic stimulation; AH, affected hemisphere; UH, unaffected hemisphere; AMT, active motor threshold; RMT, rest motor threshold; MEP, motor evoked potential; SICI, short ontracortical inhibition; Values are mean values (SD); F value and p value were calculated with one factor ANOVA.

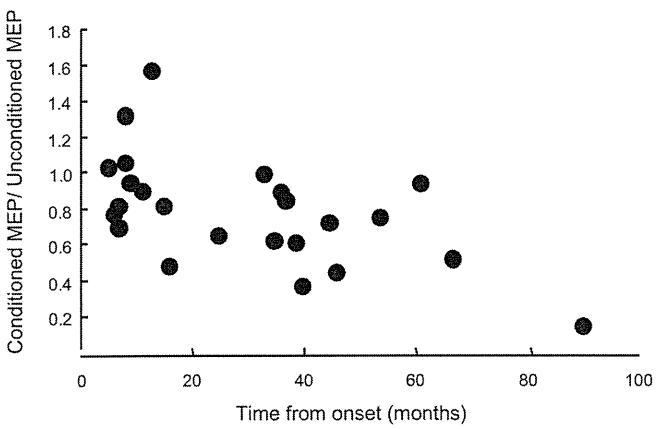

Fig. 1. The relationship between short intracortical inhibition (SICI) in the affected-hemisphere (AH) and the time course from onset (months). The SICI in the AH has a significant inverse correlation with time from onset (rs = 0.55, p = 0.006. Spearman rank correlation test).

4. Discussion

This study assessed SICI in the AH of 24 patients and the UH of 72 patients with moderate to severe hemiparetic chronic stroke (mean time from onset 28.2 months) and identified the relationships of SICI with lesion site and motor function. Few studies have assessed SICI in the AH in a large number of patients with chronic stroke. The reason for this has been the difficulty eliciting MEPs from the AH (Shimizu et al., 2002; Manganotti et al., 2008). Liepert et al. (2000) studied affected-side SICI in 11 patients in the acute phase of stroke, and Manganotti et al. (2008) studied 13 patients with moderate to severe hemiparesis from 7 to 90 days after stroke onset. Takeuchi et al. (2010) studied affected-side SICI in patients with chronic stroke, but the number of subjects was limited, and their hemiparesis was mild to moderate.

In the present study, the mean FM-U score was 28.6. Their motor function was severely impaired. In patients with severe hemiparesis, the capability of the paretic hand depends on finger extensor activity, which enables pinching and releasing of objects. In rehabilitation, it is important to restore finger extensor function (Fujiwara et al., 2009; Smania et al., 2007). Therefore, finger extensor (EDC) MEP was assessed, while previous studies assessed the first dorsal interosseous muscle or abductor pollicis brevis (Liepert et al., 2000; Takeuchi et al., 2010).

The present study showed that patients in whom MEPs were obtained from their AH had better motor function in their paretic fingers than those in whom MEPs were not obtained from the AH. The SICI of AH had inverse correlations with paretic finger motor function and time from onset.

A recent study suggested that motor function in the chronic phase is more dependent on the reorganization of alternative cortical networks than on the recovery of function of the original corticospinal pathways spared by the ischemic lesions (Swayne

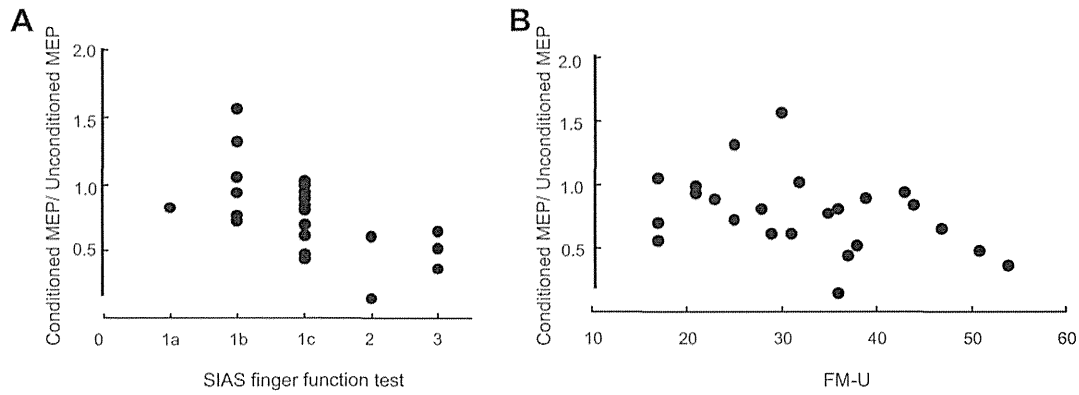

Fig. 2. (A) The relationship between the SICI in the affected-hemisphere (AH) and the Stroke Impairment Assessment Set (SIAS) finger function test score. The SICI in the AH has a significant inverse correlation with the SIAS finger function test score (Spearman rank correlation test rs = 0.61, $p = 0.001$). (B) The relationship between the SICI in the affected-hemisphere (AH) and the Fugl-Meyer test upper extremity motor score (FM-U). The SICI in the AH has a significant inverse correlation with the FM-U score (Spearman rank correlation test rs = 0.37, $p = 0.037$).

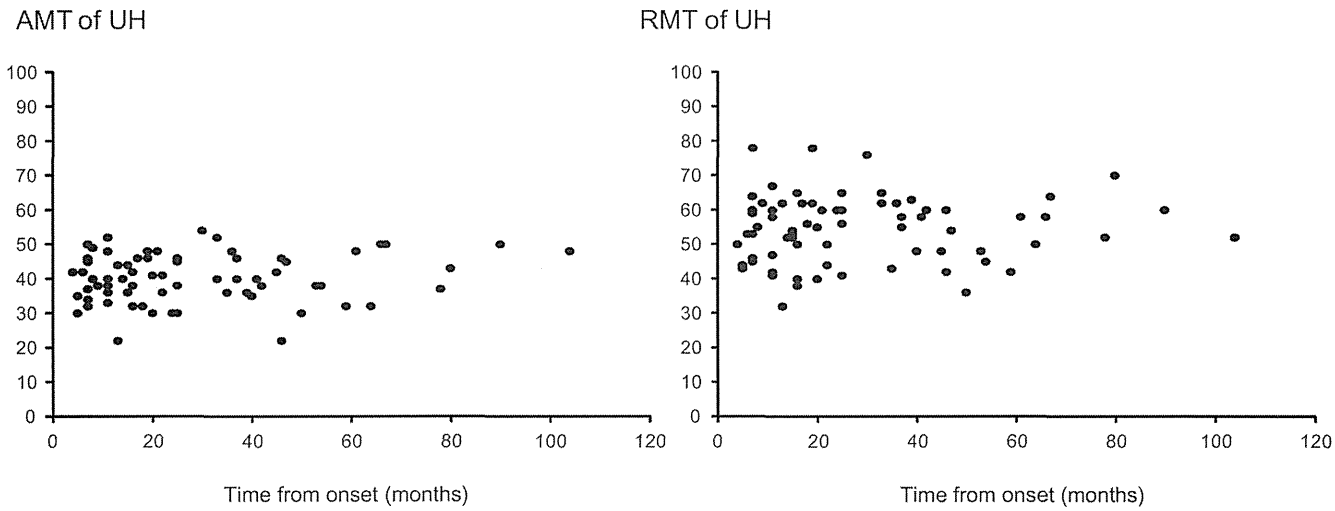

Fig. 3A. The relationships between motor threshold of unaffected hemisphere (UH) and time from stroke onset (month). Active motor threshold (AMT) of UH did not correlated with the time from stroke onset (Spearman rank correlation test rs = 0.089, $p = 0.46$). Resting motor threshold (RMT) of UH did not correlated with the time from stroke onset (Spearman rank correlation test rs = 0.035, $p = 0.78$).

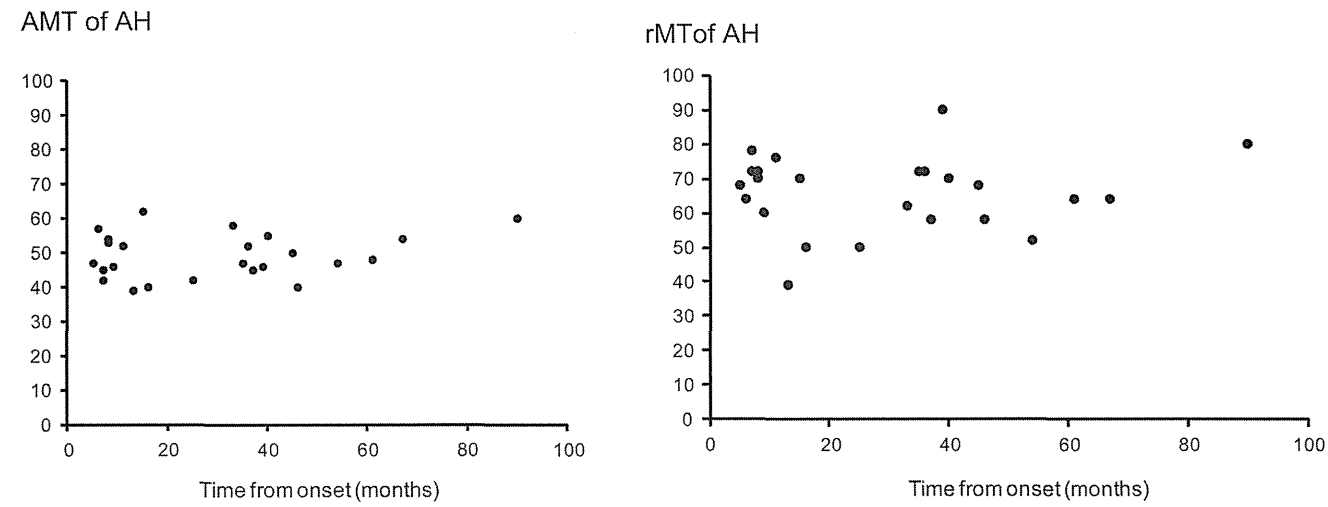

Fig. 3B. The relationships between motor threshold of affected hemisphere (AH) and time from stroke onset (month). Active motor threshold (AMT) of AH did not correlated with the time from stroke onset (Spearman rank correlation test rs = 0.124, $p = 0.56$). Resting motor threshold (RMT) of AH did not correlated with the time from stroke onset (Spearman rank correlation test rs = −0.103, $p = 0.63$).

et al., 2008). It has been suggested that intracortical disinhibition is necessary to maintain access to such additional networks, depending on the extent of disruption of the original corticospinal projection (Swayne et al., 2008). This disinhibition was found among patients with chronic stroke (over 6 months). It is suggested that patients with severe hemiparesis have the potential to induce some functional reorganization of the motor cortex even in the chronic phase, though their time window might be limited. Swayne et al. (2008) showed that corticospinal excitability of AH, measured as AMT and RMT, increased in acute phase but this increment became weaker in chronic phase (at 3 month). They also found that increased intracortical excitability continued for 6 month. In our study we assessed AMT, RMT and SICI of AH among patients with chronic stroke, their time from stroke was more than 6 months. We found disinhibition of intracortical inhibition negatively correlated with the time from stroke onset while corticospinal excitability, measures as AMT and RMT, did not correlated with the time from stroke onset. These results suggested that there may remain brain plasticity to induce functional reorganization with aid of disinhibition of intracortical inhibition in chronic phase, over 6 month from stroke onset, while it depends on the time from stroke onset.

Disinhibition of the affected side finger extensor (EDC) was also found in patients with severe hemiparesis. This disinhibition could induce facilitation of finger extension and help improve hand function with severe hemiparesis. For patients who can fully extend their fingers and move their fingers individually, it is not necessary to induce facilitation of finger extension for functional recovery. Therefore, the magnitude of intracortical inhibition may normalize in patients with mild hemiparesis.

The present study showed that disinhibition of intracortical inhibition was observed until 60 months after stroke onset among patients with severe hemiparesis. This might imply that there could be some potential to induce cortical reorganization even in patients with chronic stroke.

Studies have demonstrated that intensive hand rehabilitation changes the SICI of the AH in chronic stoke (Fujiwara et al., 2009; Liepert, 2006). Thus, the change of the SICI in the AH seems to be the result of reorganization in the primary motor cortex. These results also suggest that reorganization can be induced even in the chronic phase.

SICI of the UH had no relationships with motor function and time from stroke onset. The amount of unaffected-side SICI depended on whether the lesion was cortical or subcortical.

The abnormal disinhibition in the UH persisted in patients whose motor function remained poor (Manganotti et al., 2002). However, such a relationship between poor clinical status and increased net intracortical excitability was not observed in patients over a wide range of time points after stroke (Shimizu et al., 2002). In the present study, an increase of the value of SICI of the UH was seen in patients with cortical lesions, but not in those with subcortical lesions. Shimizu et al. (2002) reported the same result, that larger MEP amplitudes when testing SICI were seen in cortical stroke than in subcortical stroke. The change in the SICI of the UH seems to be modulated by compensatory excitation of the ipsilateral corticospinal tract (Caramia et al., 2000; Ziemann et al., 1999) and transcallosally-mediated inhibition (Shimizu et al., 2002; Bütefisch et al., 2008).

Some reports found that SICI in the UH had a correlation with motor recovery (Manganotti et al., 2008; Bütefisch et al., 2008). Di Lazzaro et al. (2009) showed that functional recovery is directly correlated with LTP-like changes in the AH and LTD-like changes in the UH and inversely correlated with the baseline excitability of the UH in acute strokes. These previous studies involved participants in the early or subacute phase of strokes.

The results of the present study did not correspond to these reports. There is a possibility that the SICI of UH is not always disinhibited, but distributed variously, and returns to the normal level over time. The present participants were patients with chronic stroke who had already undergone standardized inpatient rehabilitation during their acute and subacute phases. It was assumed that the state of SICI of the AH in the chronic phase was different from that in the acute phase.

The present study showed that the MEP amplitudes were smaller in the UH than in the control group. Nowak et al. (2007) reported that dexterity was impaired in both hands following unilateral stroke, but the mechanism of bilateral dexterity impairment remains unknown. There could be some relationship between small MEPs in the UH and impaired dexterity.

Recently, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been used as therapeutic modalities to facilitate functional recovery of chronic stroke patients. In these therapies, the basic strategy is to increase the activity of the AH or to decrease the activity of the UH. Many studies have so far adopted low frequency rTMS and cathodal tDCS to the UH to suppress its activity. However, the present study showed that SICI of the UH in the subcortical group was not as high as control SICI. The activities of the AH and UH differed in each patient. Thus, we need to evaluate patients individually to determine whether the activity of the UH is high before instituting therapeutic approaches.

It has been suggested that anatomical localization, type of stroke, and the volume of T2-hyperintense white matter could influence cerebral integrity (Kochunov et al., 2010). In this study, MRI examinations were not performed in all subjects. Furthermore, the number of patients with hemorrhagic stroke was limited. It was not possible to assess the details of lesion location or other neuroimagimg markers. More detailed analyses of lesion and white matter volumes are needed.

5. Conclusion

In conclusion, the present study provided further evidence related to affected-side and unaffected-side SICI in severe chronic stroke patients. SICI of the AH was correlated with functional recovery. However, the reorganization of the motor cortex in stroke patients was not explained solely by SICI. Therefore, further investigations involving inter-hemispheric inhibition and corticospinal activity are needed to learn more about brain plasticity.

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Comparison of the After-Effects of Transcranial Direct Current Stimulation Over the Motor Cortex in Patients With Stroke and Healthy Volunteers

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ABSTRACT

It is known that weak transcranial direct current stimulation (tDCS) induces persistent excitability changes in the cerebral cortex. There are, however, few studies that compare the after-effects of anodal versus cathodal tDCS in patients with stroke. This study assessed the after-effects of tDCS over the motor cortex in patients with hemiparetic stroke and healthy volunteers. Seven stroke patients and nine healthy volunteers were recruited. Ten minutes of anodal and cathodal tDCS (1 mA) and sham stimulation were applied to the affected primary motor cortex (M1) on different days. In healthy subjects, tDCS was applied to the right M1. Before and after tDCS, motor-evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle and silent period were measured. Anodal tDCS increased the MEPs of the affected FDI in patients with stroke as well as in healthy subjects. Cathodal tDCS increased the MEPs of the affected FDI in patients with stroke. In healthy subjects, however, cathodal tDCS decreased the MEPs. We found no significant change in the duration of the silent period after anodal or cathodal tDCS. We found that both anodal and cathodal tDCS increased the affected M1 excitability in patients with stroke. It is thought that the after-effects of tDCS are different in patients with stroke compared with healthy subjects.

KEYWORDS: cerebrovascular disease, cortical plasticity, hemiparesis, motor-evoked potential (MEP), trancranial direct current stimulation (tDCS), trancranial magnetic stimulation (TMS)

INTRODUCTION

It is known that weak transcranial direct current stimulation (tDCS) induces persistent excitability changes in the cerebral cortex. Anodal stimulation increases and cathodal stimulation decreases cortical excitability [1]. It has been confirmed in animal studies that anodal stimulation increases the excitement frequencies of nerve cells, whereas cathodal stimulation decreases the excitement frequencies of nerve cells [2,3]. Blocking *N*-methyl-D-aspartate (NMDA) receptors prevents the induction of after-effects of tDCS [4]. Therefore the after-effects of tDCS are considered to be related to synapse plasticity due to functions of NMDA receptors in addition to changes in cell membrane potentials [4,5].

Recent studies have shown that non-invasive brain stimulation enhances the beneficial effects of motor training in patients with stroke [6,7]. Hummel et al. [8,9] applied tDCS to patients with mild hemiparesis. They found that anodal tDCS to the affected primary motor cortex (M1) improved the hand function of the paretic hand. It is easy to apply tDCS to the patients

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in clinical settings because electrodes can be set on the head with a band. The after-effects of non-invasive brain stimulation depend on the state of the cortex at the time the stimulation is applied [10]. State-dependency effects of 1 Hz repetitive transcranial magnetic stimulation (rTMS) have been demonstrated in patients with migraine [11]. After a stroke, abnormally increased cortical inhibition contributes to motor dysfunction. It is supposed cathodal tDCS may decrease the excitability of cortical inhibitory interneurons and increase the motor cortex excitability among patients with stroke [12]. There are, however, few studies that compare the after-effects of anodal versus cathodal tDCS in patients with stroke. We hypothesize, therefore, cathodal tDCS may increase the motor cortex excitability in the affected hemisphere.

The aim of this study was to assess the after-effects of cathodal and anodal tDCS over the affected motor cortex in patients with subcortical stroke and healthy volunteers.

METHODS

Participants

Nine healthy volunteers (five males and four females; mean age, 34.4 years; range, 22–65 years) and seven patients with hemiparesis due to stroke (six males and one female; mean age, 64.5 years; range, 58–75 years) were recruited from National Murayama Medical Center. All participants were right-handed. One patient had a cerebral infarction and six had a cerebral hemorrhage; all patients had a subcortical lesion. Two patients had a left-hemisphere lesion and five had a right-hemisphere lesion. Table 1 shows background data on stroke patients. The finger function of the paretic hand was assessed with the Stroke Impairment Assessment Set [13], the validity and reliability of which had been already confirmed [14]. A finger motor function score of 0 means no voluntary finger movement, and score of 5 means normal. A score of 3 means that the patient can perform independent finger movements, with each finger having adequate flexion and extension. A score of 4 means the patient performs independent finger movements with mild clumsiness. The light touch sensation was checked on the palm of the hand. A sensory score of 0 indicated anesthesia and a score of 3 indicated normal. All participants gave written informed consent to the study, which was approved by the local ethical committee and conformed to the requirements of the Declaration of Helsinki. Participants had neither a psychiatric medical history nor contraindications to transcranial magnetic stimulation (TMS) [15].

Recordings

Participants were seated in a comfortable reclining chair so that the whole body, including both arms, was at rest. Surface electrodes were placed at the left first dorsal interosseous (FDI) muscle in healthy subjects and the affected FDI in patients. Signals were amplified and band-pass filtered (10 Hz to 1 kHz) by an amplifier (Neuropack® MEB 2200, Nihon-Kohden Co., Ltd., Tokyo, Japan) and stored at a sampling rate of 5 kHz on a personal computer.

Transcranial Direct Current Stimulation

tDCS was applied for 10 min at a current intensity of 1 mA through rectangular saline-soaked sponge electrodes (50 × 70 mm^2) with a battery-driven stimulator (CX-6650, Rolf Schneider Electronics, Gleichen, Germany). One stimulation electrode was placed over the M1 and the other stimulation electrode was placed above the contralateral supraorbital area. The position of M1 was confirmed through the induction of the largest motor-evoked potentials (MEPs) in the FDI muscle with constant stimulus intensity using TMS with a figure-eight stimulation coil connected to a SMN® 1200 (Nihon-Kohden Co., Ltd.). Among healthy subjects, one electrode was placed over the right M1 and the other was placed over the left side in the supraorbital area. For anodal stimulation, the anodal electrode was

TABLE 1. Demographic information of patients

Patients	Age	Sex	Time from onset (days)	Type of stroke	Affected hemisphere	Lesion	Size of lesion (mL)	SIAS finger score	SIAS sensory score (light touch)
A	62	M	297	CH	R	Putamen	14	4	2
B	60	M	327	CH	R	Putamen	18	3	2
C	58	M	33	CH	R	Putamen	9	4	2
D	75	M	127	CH	R	Thalamus	18	3	3
E	67	F	111	CH	L	Subcortical of frontal	14	4	2
F	65	M	38	CI	L	Corona radiata	4	3	2
G	62	M	70	CH	R	Thalamus	18	4	1

Note: CI, cerebral infarction; CH, cerebral hemorrhage; R, right; L, left.

placed over the right side M1, and the cathodal electrode was placed over the left supraorbital area. For cathodal stimulation, the electrodes were reversed; that is, the cathodal electrode was placed over the right M1 and the anodal electrode was placed over the left supraorbital area. Among patients with stroke, one electrode was placed on affected M1 and the other electrode was placed on contralateral supraorbital area. For anodal stimulation on patients with stroke, anodal electrode was placed on the affected M1. For cathodal stimulation, cathodal electrode was placed on the affected M1. For the sham stimulation, the current was applied for about 10 s to mimic the transient skin sensation at the beginning of actual tDCS without producing any conditioning effects on the brain. Three stimulation conditions (anodal, cathodal, and sham) were applied in each participant with a randomized sequence on different days to minimize carry-over effects. Each condition was separated from the preceding one by more than 24 h in the same participant.

Measurement of MEPs

Resting motor threshold (RMT) of the FDI was measured. For the measurement of RMT, the subject relaxed and electromyographic (EMG) silence was monitored. RMT was defined as the lowest stimulus intensity capable of inducing MEPs greater than 50 μV in at least five of 10 trials [16].

Corticospinal excitability was evaluated using suprathreshold stimulation (110% RMT). MEPs were recorded at the left FDI muscle in healthy subjects and at the paretic side in patients with stroke. Seventeen MEPs were measured and averaged at each time point, that is, before tDCS, immediately after tDCS, 10 min after tDCS, and 30 min after tDCS. The stimuli were delivered using SMN® 1200 (Nihon-Kohden Co., Ltd.) machine and a figure-eight coil with an outer winding diameter of 9 cm.

Silent Period

Six of nine healthy volunteers and six patients participated in silent period and F-wave study. A single TMS pulse was applied during isometric index finger abduction with a force of about 10%–20% maximum voluntary contraction with the help of visual feedback of the EMG activity. The duration of the silent period was defined as the time from the MEP to the return of voluntary EMG activity. Stimulus intensity was set at 110% of the RMT. Ten silent periods were measured and averaged before tDCS, immediately after tDCS, 10 min after tDCS, and 30 min after tDCS.

F-wave

In all subjects, changes in resting amplitudes of TMS-evoked MEPs following tDCS were compared with changes in the size of F-waves evoked in the relaxed FDI by supramaximal electrical stimulation of the ulnar nerve at the wrist before and after tDCS. The peak-to-peak amplitude of each of 16 F-waves was measured and then averaged before tDCS, immediately after tDCS, 10 min after tDCS, and 30 min after tDCS.

Data Analysis

We compared the baseline values of MEP with repeated measure ANOVA. All data were analyzed with the general linear model three-way mixed ANOVA with factors of time (before and at intervals after tDCS), stimulation (anodal, cathodal, and sham tDCS), and category (healthy subjects and stroke subjects). Conditional on a significant F value, post-hoc tests were performed with using paired and unpaired t-tests. Values were considered statistically significant when $p < 0.05$. Statistical analysis was performed with SPSS 15.0J (SPSS Japan, Tokyo, Japan).

RESULTS

Motor-Evoked Potentials

No participant experienced any side effects from the stimulation. RMTs were expressed as the percentage of maximum output of the magnetic stimulator. The mean (SE) RMT value of healthy subjects was 49.1% (2.3%), and the mean RMT value of the stroke group was 70.2% (4.2%). The difference was significant with unpaired t-test ($p = 0.001$).

The mean amplitude of MEPs (SE) in healthy subjects before anodal, cathodal, and sham tDCS were 0.40 (0.03), 0.61 (0.11), and 0.59 (0.11) mV, respectively. The mean amplitude of MEPs (SE) in patients with stroke before anodal, cathodal, and sham tDCS were 0.22 (0.07), 0.24 (0.06), and 0.22 (0.05) mV, respectively. There were no significant differences in mean MEP amplitude before anodal, cathodal, and sham tDCS in healthy subjects ($F_{2,16} = 1.644, p = 0.224$) and patients with stroke ($F_{2,12} = 0.13, p = 0.877$).

The changes of MEPs were expressed as the ratio to the mean value of before tDCS in each subject. Figure 1 shows the change of MEPs induced by anodal and cathodal tDCS and sham stimulation among the nine healthy subjects. Figure 2 shows the change of MEPs induced by anodal and cathodal tDCS and sham stimulation among the seven patients with stroke. Three-way mixed ANOVA showed significant interaction of time